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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/516,729
Filing Date: December 06, 2004
Appellant(s): ZLOKOVIC, BERISLAV V.

Gary R. Tanigawa
Nixon & Vanderhye P.C.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 23 June 2009 appealing from the Office action mailed 12 December 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Grammas, P. et al. "Alzheimer Disease Amyloid Proteins Inhibit Brain Endothelial Cell Proliferation in vitro" Dementia vol 6 (1995), pp.126-130

Mulliken, J.B. et al. "In vitro characteristic of endothelium from hemangiomas and vascular malformations" Surgery Vol 92 no. 2 (1982) pp.348-353

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-2, 5-6, and 27-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grammas 1995 (Dementia 6:126 – 130) in view of Mulliken 1982 (Surgery 92(2):348 – 353).

Grammas teaches that it is well-known that patients with Alzheimer's disease (AD) have disease-related changes in cerebral vasculature. Such changes include "significant reduction in vascular density and capillary diameter as well as deformities of angioarchitecture. Accumulation of Aβ in blood vessels causes degeneration of endothelial and smooth muscle cells and thus could underlie changes in cerebral blood flow and vascular rupture" (Grammas, p. 126, first paragraph of Introduction; citations omitted). Grammas teaches that Aβ, purified from the brains of human patients diagnosed with Alzheimer's disease, inhibits the replication of cerebral endothelial cells cultured *in vitro*. Specifically, Grammas teaches that when Aβ from human Alzheimer's patients is contacted with rat brain endothelial cells, the rate of proliferation of those cells is decreased as compared to control-treated cells. See Grammas, p. 127 for methods of purifying Aβ from tissue and cell culture methods as well as p. 128 for the results of the experiments. As proliferation of endothelial cells derived from blood vessels is required for angiogenesis, the reference is on point to claim the "defective angiogenesis" limitation of claims 1, 27, 33, and 39. The Aβ protein was purified from human patients diagnosed with Alzheimer's disease, which is on point to claims 1, 2, 27, 33, and 39. The endothelial cells were cultured to provide derived cells, which is on point to claims 4, 27, and 33. The cells have defective response to angiogenic signaling (i.e., the signals responsible for control of growth and proliferation of these endothelial cells; see paragraph spanning pp. 128 - 129), which is on point to claims 5, 28, and 34. However, while Grammas teaches contacting cultured rat cerebral endothelial cells with Aβ from human Alzheimer's patients, the reference does not teach obtaining and culturing *human* endothelial cells from Alzheimer's patients and subsequently determining the degree of defective angiogenesis, as encompassed by claims 1, 27, and 33.

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Mulliken teaches taking tissue from human hemangiomas and blood vessel malformations and culturing the tissue in medium. Specifically, at p. 348 Mulliken teaches obtaining the tissue surgically and the methods used to culture the tissue. Endothelial tissue was specifically selected whereas other tissue was discarded. The reference also teaches that hemangiomas, which comprise vascular endothelium, undergo tube-formation *in vitro*. The

authors report this phenomenon is *in vitro* angiogenesis (see for example p. 350, second column), which is on point to determination of defective angiogenesis as recited in claims 1, 27, 33, and 39. Mulliken also reports that capillaries from human tissue can routinely be cultured *in vitro* and that these methods are suitable for determining which specific abnormalities are present in the endothelium sample. However Mulliken does not teach obtaining endothelial tissue from patients with neurodegenerative disease or another cognitive impairments in general, or Alzheimer's disease in particular.

It would have been obvious to one of ordinary skill in the art to modify the methods of Grammas to include the step of culturing human endothelial cells derived from the brain, as taught by Mulliken, with a reasonable expectation of success. Specifically, it would have been obvious to one of ordinary skill in the art to further culture tissue comprising endothelial cells derived from human brains as taught by Grammas and determine the degree of defective angiogenesis. The motivation to do so would be to determine the degree of defective angiogenesis and endothelial cell proliferation in the same tissue from the same species of mammal as Grammas had already obtained human brain samples from 8 Alzheimer patients (page 127). It would be reasonable to expect success, as the reference by Grammas indicates that Aβ from human Alzheimer's patients results in defective proliferation of endothelial cells from blood vessels (i.e., angiogenesis), and the reference by Mulliken teaches that it is routine to culture endothelial cells from human tissue and teaches that this method shows the changes in endothelial cells phenotypes. Furthermore, the reference by Grammas clearly teaches one of ordinary skill in the art that Alzheimer's disease was known to induce changes in cerebral vasculature of patients with the disease. Therefore, one of ordinary skill in the art would have been motivated to select tissue from a human patient with Alzheimer's, and additionally would have had a reasonable expectation of success in determining that the endothelium from such patients is defective in angiogenesis, or has inappropriate senescence, since the reference teaches that contacting endothelial tissue with Aβ leads to inappropriate angiogenesis.

Modifying the teachings of Grammas in this manner would lead to the invention set forth in claims 1, 27 – 28, 33 – 34, and 39. Claims 5 – 6, 29 – 32, 35 – 38, and 40 are included in this rejection as these claims do not require any additional method steps (such as detecting anoikis, apoptosis, or programmed cell death) or starting materials, but merely recite features of the cells which are necessarily present. Note that inherent features need not be recognized at the time

of invention or in the prior art (MPEP §2112(II)), and that implicit or inherent disclosures are to be considered in determinations of obviousness (MPEP § 2144.01).

(10) Response to Argument

Appellant argues, on pp. 5-6 of the brief, that the combination of the two references cited by the examiner fails to either teach or render obvious the claimed methods. Particularly, appellant argues that neither reference teaches or makes obvious the step of obtaining endothelial tissue from a human subject with Alzheimer's disease, which is either explicitly required by, or encompassed in, each of the independent claims under appeal. Appellant did not separately argue the patentability of dependent claims, but rather indicated that these stand or fall with the independent claims (see brief, p. 3 final sentence and p. 5 first complete paragraph).

The examiner acknowledges that neither reference explicitly teaches the step of obtaining tissue from a human subject with Alzheimer's disease. However, the reference by Grammas clearly renders obvious this step. Grammas provides detailed descriptions of the well-known changes in cerebral vasculature seen in AD patients; see Introduction, first paragraph. This suggests to one of ordinary skill in the art that disease-related changes in cerebral vasculature will be apparent in patients with Alzheimer's disease. Grammas also describes the results of specific experiments, which show that contacting vascular endothelial tissue from normal (not subject to Alzheimer's disease or an animal model thereof) rat brain with Aβ obtained from AD patients brains leads to decreased proliferation of these vascular endothelial cells (see p. 128 for results). Interestingly, Grammas also teaches that synthetic Aβ, obtained from a commercial vendor, does not have the same effect. One of ordinary skill in the art would reasonably conclude that a secondary structure, i.e. specific to the Aβ-containing aggregates, or plaques, is responsible for the observed decrease in vascular endothelial cell proliferation. Given that Grammas teaches that vascular endothelial cells are damaged in Alzheimer's disease, and that Aβ-containing plaques from human AD patients are able to induce decreases in vascular endothelial cell proliferation, one of ordinary skill in the art would have found it obvious to perform this assay on the same type of cells obtained from human AD patients, rather than from physiologically normal rats as taught by Grammas. The motivation to do so would be to accurately diagnose Alzheimer's disease. One of ordinary skill in the art would reasonably expect that the endothelial cells from the Alzheimer's disease patients would

have defective angiogenesis when cultured, since Grammas teaches that A) AD is characterized by changes in cerebral vasculature (p. 126) and B) decreases in angiogenesis are induced by toxic Aβ aggregates. Therefore, the step of obtaining vascular endothelium from patients with Alzheimer's disease, as encompassed by each of the present independent claims, would have been obvious to one of ordinary skill in the art at the time the invention was made. The reference by Milliken provides the artisan of ordinary skill instructions on how to culture human vascular cells and determine the degree of *in vitro* angiogenesis.

Appellant also argues, at p. 6 of the brief, that the observed result, namely that there was defective angiogenesis in vascular tissue obtained from AD patients, was surprising. Given the extensive teachings of Grammas, who teaches both that vascular tissue from AD patients is damaged and that Aβ from AD patients can induce changes in proliferation of normal vascular tissue, the examiner is of the opinion that such an observation would not have been surprising, but rather would have been expected.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Daniel E. Kolker/

Primary Examiner, Art Unit 1649

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